

### **REMARKS**

With this amendment, claims 1, 3, 4, 9-14, 16, 20, 22, 26, 28, 29, 34-37, 41, 52-57, and 71 have been amended to clarify that which Applicants regard as their invention. Claims 2, 27, 51 and 62-70 have been cancelled. Claims 1, 9-13, 16, 20, 26, 34-37, 41, 52-57, and 71 have been amended to delete the term “organism” in favor of “species”. Claims 1, 26, 52, and 71 have been amended to recite a phenotypic data structure that **comprises** a difference in a phenotype between different strains of a species. Claims 1, 26, and 52 have been further amended to recite that an amount of a genome that is included in a locus in a plurality of loci is predetermined. Claims 1, 12, 14, 16, 26, 52 and 71 have been amended to recite a genotypic data structure that **comprises** a variation (or a plurality of variations) of at least one component of a locus between different strains of a species. Claims 3, 4, 28 and 29 have been amended to correct for antecedent basis as a result of the cancellation of claims 2 and 27. Claim 54 has also been amended to correct for antecedent basis. Claims 9, 11, 34, and 53 have been amended to recite that each element in a phenotypic data structure corresponds to a difference in a phenotype. New claims 72-77 have been added to more particularly recite certain aspects of the present invention. No new matter has been added by virtue of these claim amendments and new claims.

Upon entry of the present amendments, claims 1, 3-26, 28-50, 52-61, and 71-77 will be pending in the above-identified application.

### **INFORMATION DISCLOSURE STATEMENTS**

Applicants have submitted three information disclosure statements in the above-identified case. With this response, a fourth information disclosure statement has been submitted. The first information disclosure statement, containing references AA through AV, was submitted at the time of filing on December 11, 2001. The second information disclosure statement, containing references AW through BJ was submitted on August 7, 2002. The third information disclosure statement, containing references BK through BM, was submitted on September 27, 2002.

In the October 21, 2003 Office Action, the examiner enclosed signed off copies of the list of references cited in the second and third information disclosure statements (references AW through BM) but not the list of references cited in the first information disclosure

statement (references AA through AV). Attorneys for Applicants called Examiner C. Dune Ly on November 25, 2003 to notify the Examiner of this omission. In this telephone conference, Examiner Ly agreed to consider references AA through AV in the next office action. Applicants note that reference AA is identical to reference BJ and therefore respectfully request that reference AA be stricken so that it is not printed twice on the cover of any patent that may issue in the above identified case.

**THE PROVISIONAL STATUTORY 35 U.S.C. § 101 DOUBLE PATENTING REJECTION  
SHOULD BE WITHDRAWN**

The PTO has provisionally rejected claims 1 and 9 on statutory 35 U.S.C. § 101 double patenting grounds for allegedly claiming the same invention as that of claims 1 and 2 of copending Application No. 09/737,918.

Section 804 II. A. of the Manual of Patent Examining Procedure ("M.P.E.P.", Eight Edition, August 2001, February 2003 revision) states that statutory double patenting does not exist if there is an embodiment of the invention that falls within the scope of a claim in one application but does not fall within the scope of the corresponding claim in the other application. For example, the invention defined by a claim reciting a compound having a "halogen" substituent is not identical to or substantively the same as a claim reciting the same compound except having a "chlorine" substituent in place of the halogen because "halogen" is broader than "chlorine." Thus, double patenting in this example is without basis according to section 804 II. A. of the M.P.E.P.

Applicants have revised claim 1 of the above-identified application to include the phrase "and wherein an amount of said genome that is included in each locus in said plurality of loci is predetermined." The feature of using a predetermined size for each locus is discussed on page 15, line 19, through page 16, line 4, of the specification. This feature is not disclosed in copending Application No. 09/737,918. Accordingly, Applicants respectfully request that the statutory double patenting rejection be withdrawn.

**THE PROVISIONAL NON-STATUTORY 35 U.S.C. § 101 DOUBLE PATENTING  
REJECTION SHOULD BE WITHDRAWN**

The PTO has provisionally rejected claims 1, 9-13, 16, 17, 24-26, 34-38, 41, 42, and 48-61 on 35 U.S.C. § 101 non-statutory double patenting grounds for allegedly claiming the same invention as that of claims 1-32 of copending Application No. 09/737,918. With

respect to claim 51, the provisional rejection is moot because Applicants have cancelled the claim. Although Applicants disagree with the PTO's reasoning, in order to expedite prosecution, Applicants have authorized the enclosed terminal disclaimer. Therefore, Applicants respectfully request that the non-statutory double patenting rejection be withdrawn.

THE 35 U.S.C. § 102 REJECTION SHOULD BE WITHDRAWN

The PTO has rejected claims 1-10, 12, 13, and 18 under 35 U.S.C. § 102(b) as allegedly being anticipated by Luo and Kearsy, 1992, "Interval mapping of quantitative trait loci in an F<sub>2</sub> population," *Heredity* 69, pp. 236-242 (hereinafter "Luo"). With respect to claim 2, the rejection is moot because the claim has been cancelled. With respect to claims 1, 3-10, 12, 13, and 18, Applicants respectfully traverse the rejection.

The standard for anticipation under 35 U.S.C. §102 is strict identity. Anticipation under §102 can only be established by a prior art reference that teaches each and every element of the claimed invention. *Structural Rubber Products Co. v. Park Rubber Co.* 223 USPQ 1264 (1984). Applicants respectfully submit that Luo fails to recite each and every limitation of pending claims 1, 3-10, 12, 13, and 18.

Luo is directed to a method of mapping and characterizing quantitative trait loci using F<sub>2</sub> data derived from inbred line crosses as well as marker information. In Luo, two inbred lines, P<sub>1</sub> and P<sub>2</sub>, are crossed in order to create linkage disequilibrium between loci that differ in the two inbred lines. This linkage disequilibrium in turn creates associations between marker loci and linked segregating QTLs. An overview of the techniques used by Luo is found in Chapter 15 of Lynch and Walsh, *Genetics and Analysis of Quantitative Traits*, Sinauer Associates, Inc., Sunderland, Massachusetts, 1998 (reference BN of the attached supplemental information disclosure statement) as well as Doerge, 2003, *Nature Reviews Genetics* 3, pp. 43-52 (reference BO of the attached supplemental information disclosure statement). Central to these techniques is the modeling of segregated markers and QTL in a single population.

In the October 21, 2003 office action, the PTO equates the alleles respectively found in the two inbred lines P<sub>1</sub> and P<sub>2</sub> of Luo to the phenotypic data structure recited in claim 1. Further, the PTO equates the marker linkage map of Luo (in which a genome is separated into a series of chromosomal segments each of which is flanked by two marker loci) to the

genotypic data structure of claim 1 as amended. As will be discussed below, the claimed phenotypic data structure and the claimed genotypic data structure have no such counterpart in Luo.

*Luo does not disclose the claimed phenotypic data structure.* Applicants have amended claim 1 to recite a phenotypic data structure that comprises a difference in a phenotype between different strains of a species.

Page 14 of the specification provides the following example of the construction of a phenotypic data structure using five mouse strains. Consider the phenotypic data for lifespan:

Strains	Lifespan (days)
A/J	777
AKR/J	282
C3H/HeJ	510
C57BL/6J	895
DBA/2J	568

A phenotypic distance matrix that tracks the lifespan for these five species members has the form:

P	A/J	AKR/J	C3H/HeJ	C57BL/6J	DBA/2J
A/J	0	495	267	118	209
AKR/J	495	0	228	613	286
C3H/HeJ	267	228	0	385	58
C57BL/6J	118	613	385	0	327
DBA/2J	209	286	58	327	0

The phenotypic data structure is the non-redundant, non-diagonal elements of this matrix (P= 495, 267, 118, 209, 228, 613, 286, 385, 58, 327). As such, the phenotypic data structure comprises a difference in a phenotype between different strains of the species as recited in amended claim 1. For example, the phenotypic data structure includes the value 495, which

represents the difference in days between the lifespan of the AKR/J mouse strain and the A/J mouse strain.

Luo does not have a data structure that represents the difference in a phenotype between different strains of a species because Luo simply does not compute a difference in a phenotype between different strains of a species. In particular, Luo does not compute the difference between the alleles  $Q$  associated with line  $P_1$  and the alleles  $q$  associated with line  $P_2$ . Rather, lines  $P_1$  and  $P_2$  are crossed in Luo and the  $F_2$  family is considered. See, for instance, page 237, second column, lines 5-8 of Luo which state “[i]n the  $F_2$  family discussed previously, a sample of  $n$  individuals is scored for their quantitative phenotype, denoted by  $Y = \{y_1, y_2, \dots, y_n\}$ , and their marker genotype.” This data is then used to identify QTL in the genome of the  $F_2$  generation using the methods discussed in Luo.

*Luo does not disclose the claimed genotypic data structure.* Claim 1 recites a genotypic data structure that comprises a variation of at least one component of the locus between different strains of a species. Page 16, line 5, through page 18, line 12, of the specification provide an example of a genotypic data structure. In the example, the claimed variation is counts of the polymorphic differences between strains for a locus  $L$  that contains  $M$  genetic variations, such as SNPs. An individual variation matrix  $S^x$  is established for each variation in every position  $x$  within a locus  $L$ . In each such matrix,  $S^x$ , the  $i^{\text{th}}$  row and the  $j^{\text{th}}$  column are associated with the allele value  $l^x(i)$  for strain  $i$  and the allele value  $l^x(j)$  for strain  $j$  at locus position  $x$  according to the following rule:

$$\begin{aligned} S^x(i, j) &= 1/2 \text{ if } l^x(i) = \emptyset \text{ or } l^x(j) = \emptyset \\ &= 0 \text{ if } l^x(i) = l^x(j) \\ &= 1 \text{ if } l^x(i) \neq l^x(j) \end{aligned}$$

where  $\emptyset$  indicates that the allelic value for strain  $i$  at locus position  $x$  is not known at the present time. Therefore, if the alleles for two strains  $i$  and  $j$  are identical at position  $x$ , the entry in the individual variation matrix for  $x$  is:

$$S^x(i, j) = S^x(j, i) = 0$$

and if the two alleles are different, a “1” is entered. In cases where allelic information is known the corresponding entry is set equal to one half. Thus, each individual variation matrix *S* contains elements that take on one of three values: 0, ½, or 1. To illustrate, a variation matrix *S* that tracks an individual locus position *x* for five strains (M1 through M5) of a species can have the form:

<b>S</b>	<b>M1</b>	<b>M2</b>	<b>M3</b>	<b>M4</b>	<b>M5</b>
<b>M1</b>	0	0.5	0.5	1	0
<b>M2</b>	0.5	0	0.5	0	1
<b>M3</b>	0.5	0.5	0	1	1
<b>M4</b>	1	0	1	0	0.5
<b>M5</b>	0	1	1	0.5	0

In one embodiment of the present invention, in order to assemble the overall genotypic matrix for this locus, each individual variation matrix *S* within the locus *L* selected in processing step 204 is summed. See, for example, Applicants’ specification, page 18, lines 1-12.

Claim 1 recites that the genotypic data structure comprises a variation of at least one component of the locus between different strains of the species. Thus, following the example described above, the genotypic data structure of claim 1 includes the values of at least one variation matrix *S*.

Luo does not have the claimed genotypic data structure. While the marker linkage map of Luo may indeed be considered a genotypic data structure, it does not include variation of at least one component (location) of a locus between different strains of the species as recited in claim 1 as amended.

Claims 3-10, 12, 13 and 18 ultimately depend from claim 1 and is therefore patentable over Luo for at least the same reasons that claim 1 is patentable over Luo.

For all of the above-identified reasons, Applicants respectfully request that the rejection of claims 1, 3-10, 12, 13, and 18 be withdrawn.

THE 35 U.S.C. § 103 REJECTION SHOULD BE WITHDRAWN

The PTO has rejected claims 1-13, 16, 18, 19, 23-28, 41, 43, 44, 48-57, 59-61, and 71 under 35 U.S.C. § 103(a) as allegedly being anticipated by Luo taken with United States Patent Number 6,132,724 to Blum (hereinafter “Blum”). With respect to claims 2, 27, and 51, the rejection is moot because the claims have been cancelled. With respect to claims 1, 3-13, 16, 18, 19, 23-26, 28, 41, 43, 44, 48-50, 52-57, 59-61, and 71, Applicants traverse the rejection.

To reject claims in an application under 35 U.S.C. § 103, the PTO bears the initial burden of establishing a prima facie case of obviousness. *In re Bell*, 26 USPQ2d 1529, 1530 (Fed. Cir. 1993). In order to establish prima facie obviousness, the prior art, either alone or in combination, must teach or suggest each and every limitation of the rejected claims. *In re Vaeck*, 20 USPQ2d 1438 (Fed. Cir. 1991); *In re Royka and Martin* 180 USPQ 580 (C.C.P.A. 1974); and *In re Wilson* 165 USPQ 494 (C.C.P.A. 1970).

Claims 1, 26, 52, and 71 each recite a phenotypic data structure that comprises a difference in a phenotype between different strains of a species. Further, claims 1, 26, 52, and 71 each recite a genotypic data structure that comprises a variation of at least one component of the locus between different strains of a species. As discussed in response to the 35 U.S.C. § 102 rejections above, Luo does not disclose such data structures. Blum also does not teach or suggest the claimed data structures. Therefore, claims 1, 26, 52, and 71 are patentable over the combination of Luo and Blum. Each of the remaining rejected claims depend from one of claims 1, 26, or 52 and are thus patentable over the combination of Luo and Blum for at least the same reasons that claims 1, 26, and 52 are patentable over Blum.

Claims 11, 16, 19, and 44 are patentable over the combination of Luo and Blum for the following additional reasons. The PTO indicates that column 7, lines 35-61, of Blum teaches phenotypic data structures and/or genotypic data structures in which each element in the structures represents a **difference** between a first and second cluster of strains of a species as respectively recited in claims 11 and 16. This is not the case. The cited section of Blum states “[t]he MCMI-II assessed schizoid/avoidant cluster compared to other Axis II diagnostic clusters (antisocial, narcissistic, paranoid) significantly correlated with alcohol abuse scales.” This cannot be equated to Applicants’ claims 11 and 16 for two reasons. First, claims 11 and 16 recite “clusters of **strains**” of a species. Blum does not disclose the comparison of strains of a species. Second, claims 11 and 16 are directed to a **difference**

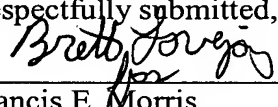
between a first and second cluster of strains of a species. Blum is not directed to data structures that track **differences** in species, much less differences in clusters of strains. Claims 19 and 44 are directed to single nucleotide polymorphism, a genetic feature that is not referred to in column 7, lines 35-61, of Blum.

CONCLUSION

Applicants respectfully request entry of the foregoing amendments and remarks into the file of the above-identified application. Applicants believe that each ground for rejection has been successfully overcome or obviated, and that all the pending claims are in condition for allowance. Withdrawal of the Examiner's rejections and allowance of the application are respectfully requested.

Date: December 24, 2003

Respectfully submitted,

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\_\_\_\_\_  
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Enclosure





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ASSIGNOR:

GROUPE, ANDREW

DOC DATE: 04/04/2002

ASSIGNOR:

PELTZ, GARY ALLEN

DOC DATE: 03/18/2002

ASSIGNOR:

USUKA, JONATHAN ANDREW

DOC DATE: 03/18/2002

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SERIAL NUMBER: 10015167

FILING DATE: 12/11/2001

PATENT NUMBER:

ISSUE DATE:

012571/0790 PAGE 2

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A. Patent Application No.(s)

U.S. Serial No. 10/015,167, filed December 11, 2001

Attorney Docket No. R0108B-CIP

B. Patent No.(s)

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ASSIGNMENT

RBS No. R0108B-CIP

WHEREAS, We, Andrew Grupe, Gary Allen Peltz and Jonathan Andrew Usuka ("Assignors") having the respective addresses indicated below, have invented certain subject matter entitled **"System and Method for Predicting Chromosomal Regions That Control Phenotypic Traits"** (the "Invention"), described in patent application U.S. Serial No.10/015,167, filed December 11, 2001, for Letters Patent of the United States of America (the "Application");

AND WHEREAS, Syntex (U.S.A.) LLC, a company of Delaware, having an address at 3401 Hillview Avenue, Palo Alto, California 94304 ("Syntex"), desires to perfect its right to the Invention and in the Letters Patent(s) to be obtained therefor from the United States of America and all countries foreign thereto;

NOW, THEREFORE, in exchange for good and valuable consideration, the receipt and sufficiency of which are hereby acknowledged, Assignors acknowledge Syntex's interest in the Invention and hereby assign to Syntex for the United States of America and all countries foreign thereto all our rights, title and interest, including all rights under the Paris Convention for the Protection of Industrial Property, in the Invention, as described and claimed in patent application U.S. Serial No.10/015,167, or in any subsequent patent application(s) filed under 35 U.S.C. §111(a), claiming benefit of said Application under 35 U.S.C. §119(e), or 35 U.S.C. §120, or in any continuation, continuation-in-part, continued prosecution application, divisional, substitute, reissue, reexamination or extension thereof and any legal equivalent thereof in a country foreign to the United States of America; the Invention, application and Letters Patent(s) to be owned by Syntex, its successors, assigns and legal representatives, to the full end of the term for which such Letters Patent(s) may be granted.

Assignors hereby covenant that they have the full right to convey the entire interest assigned herein and have not executed and will not execute any agreement in conflict herewith.

Assignors further covenant to execute and deliver upon request and without undue delay, to Syntex, its successors, assigns and legal representatives, all lawful documents necessary or desirable to effect this assignment and perfect the title to the Invention, Application and Letters Patent(s) and all foreign patents and applications claiming priority thereto.

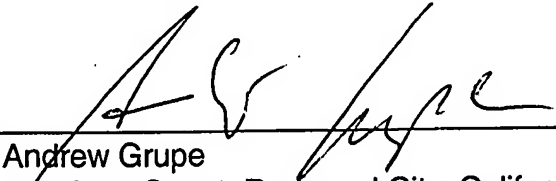
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ASSIGNMENT

RBS No. R0108B-CIP

This assignment is effective as of the earlier of the date of execution of this document or the filing date accorded by the United States Patent and Trademark Office to patent application U.S. Serial No.10/015,167, as indicated in the Filing Receipt for said Application.

I have read and understand this Assignment document for the Application, and agree hereto, as indicated by my signature as set forth below.

Signature  Date 4/04/02  
Andrew Grupe  
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Signature  Date 3/18/02  
Gary Allen Peltz  
110 Danbury Lane, Redwood City, California 94061

Signature  Date 3/18/02  
Jonathan Andrew Usuka  
220 Chestnut Avenue, Palo Alto, California 94306

# CALIFORNIA ALL-PURPOSE ACKNOWLEDGMENT

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County of Santa Clara

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On 18-March-2002, before me, Christina G. Myers, Notary Public,  
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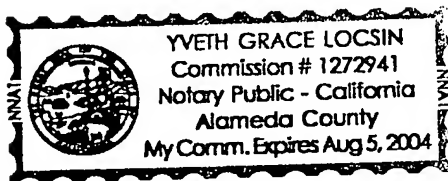
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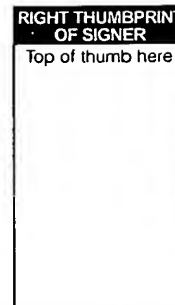
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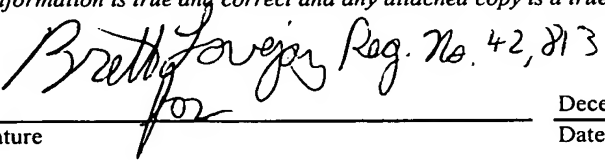




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5. Name and address of party to whom correspondence concerning document should be mailed: PENNIE & EDMONDS LLP 1155 Avenue of the Americas New York, New York, 10036-2711		6. Number of applications and patents involved: <u>1</u> 7. Total fee (37 CFR 3.41):.....\$ 40.00 Please charge to the deposit account listed in Section 8. 8. Deposit account number: <u>16-1150</u>	
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9. Statement and signature.  <i>To the best of my knowledge and belief, the foregoing information is true and correct and any attached copy is a true copy of the original document.</i>  <div style="display: flex; justify-content: space-between;"><div>Francis E. Morris Name of Person Signing</div><div>24,615 Reg. No.</div><div> Signature</div><div>December 24, 2003 Date</div></div>			
Total number of pages including cover sheet:			3

Mail documents to be recorded with required cover sheet information to:  
Mail Stop Assignment Recordation Services  
Director of the United States Patent and Trademark Office  
P.O. Box 1450  
Alexandria, VA 22313-1450

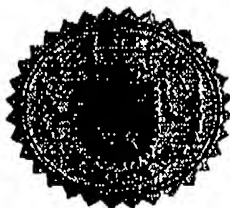


# Delaware

PAGE 1

*The First State*

I, HARRIET SMITH WINDSOR, SECRETARY OF STATE OF THE STATE OF DELAWARE, DO HEREBY CERTIFY THE ATTACHED IS A TRUE AND CORRECT COPY OF THE CERTIFICATE OF AMENDMENT OF "SYNTEX (U.S.A.) LLC", CHANGING ITS NAME FROM "SYNTEX (U.S.A.) LLC" TO "ROCHE PALO ALTO LLC", FILED IN THIS OFFICE ON THE TWENTY-THIRD DAY OF DECEMBER, A.D. 2002, AT 4 O'CLOCK P.M.



3205906 8100

030585329

*Harriet Smith Windsor*

Harriet Smith Windsor, Secretary of State

AUTHENTICATION: 2627285

DATE: 09-11-03

STATE OF DELAWARE  
SECRETARY OF STATE  
DIVISION OF CORPORATIONS  
FILED 04:00 PM 12/23/2002  
020794267 - 3205906

## CERTIFICATE OF AMENDMENT

OF

SYNTEX (U.S.A.) LLC

1. The name of the limited liability company is, upon the effective time of this amendment, Roche Palo Alto LLC.

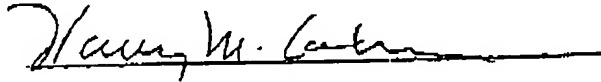
2. The Certificate of Formation of the limited liability company is hereby amended as follows:

The paragraph labeled "FIRST" is changed to read, The name of the limited liability company formed hereby is Roche Palo Alto LLC.

The heading is changed to read, CERTIFICATE OF FORMATION OF ROCHE PALO ALTO LLC.

3. This Certificate of Amendment shall be effective on 12:01 am, January 1, 2003.

IN WITNESS WHEREOF, the undersigned has executed this Certificate of Amendment of Syntex (U.S.A.) LLC this 20<sup>th</sup> day of December, 2002.



Nancy M. Cohen  
Vice President, Secretary

05084 - 2/12/2002 CT System Online

COHEN N 119635-01  
12/19/02 at 11:14 AM

TOTAL P.02